

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-11 (cancelled).

12 (currently amended). An isolated polypeptide which

(a) consists of residues 234-1791 of SEQ ID NO:2; or

(b) is at least ~~99%~~ 95% identical to a polypeptide of

(a), but differs from the polypeptide of (a)

~~therefrom by one or more insertions and/or~~

~~deletions and/or substitutions,~~

solely by

(b1) deletion of 1-10 residues from, or addition of 1-10 residues to, the amino terminal, and/or

(b2) deletion of 1-10 residues from, or addition of 1-10 residues to, the carboxy terminal and/or

(b3) one or more conservative substitutions,

wherein said polypeptide

i) has a proteolytic activity against Insulin Like Growth Factor Binding Protein 5 (IGFBP-5); ~~and/or~~

ii) ~~is recognised by an antibody, or a binding fragment thereof, which recognizes a mature pregnancy associated plasma protein A-2 (mature PAPP-A2) consisting of the amino acid sequence shown as amino acids 234-1791 of SEQ ID NO:2.~~

13-17 (cancelled).

18. (previously presented). The polypeptide of claim 12, wherein said polypeptide is a recombinant polypeptide.

19. (previously presented). The polypeptide of claim 12, wherein the polypeptide is free of human proteins, or other

proteins naturally associated with said polypeptide.

20-29 (cancelled).

30 (withdrawn). A method for detecting pregnancy associated plasma protein A-2 (PAPP-A2), or measuring the level of PAPP-A2, in a biological sample obtained from an individual, said method comprising the steps of

- i) obtaining a biological sample from said individual,
- ii) detecting PAPP-A2 in said sample by detecting a polypeptide according to claim 12.

31 (withdrawn). Method of claim 30, said method comprising the further step of comparing the PAPP-A2 or the level of PAPP-A2 detected in step ii) with a predetermined value selected from the group consisting of

- i) a predetermined amount and/or concentration of PAPP-A2; and/or
- ii) a predetermined amount and/or concentration of PAPP-A2 mRNA; and/or
- iii) a predetermined PAPP-A2 specific protease activity.

32 (withdrawn). Method of claim 31, wherein said predetermined value is indicative of a normal physiological condition of said individual.

33 (withdrawn). The method of claim 30, wherein said biological sample is selected from the group consisting of blood, urine, pleural fluid, oral washings, tissue biopsies, and follicular fluid.

34 (withdrawn). The method of claim 30, wherein said level of PAPP-A2 is measured as PAPP-A2 specific protease activity.

35 (withdrawn). The method of claim 30, wherein said level of PAPP-A2 is measured as amount of PAPP-A2 protein.

36 (withdrawn). The method of claim 30, wherein said level of PAPP-A2 is measured as amount of PAPP-A2 messenger RNA.

37 (withdrawn). The method of claim 35, wherein said amount of PAPP-A2 protein is measured by immunochemical analysis.

38 (withdrawn). The method of claim 37, wherein said amount of PAPP-A2 protein is detected by at least one monoclonal antibody.

39 (withdrawn). The method of claim 30, wherein said PAPP-A2 protein is detected in a complex comprising at least one additional polypeptide.

40 (withdrawn). The method of claim 30, wherein said PAPP-A2 is detected as a PAPP-A2 monomer.

41 (withdrawn). The method of claim 30, wherein said PAPP-A2 is detected as a PAPP-A2 dimer.

42 (withdrawn). A method of diagnosing a clinical condition in an individual, said method comprising the steps of

i) performing the method of claim 30, and

ii) diagnosing the clinical condition.

43 (withdrawn). Method of claim 42, wherein said clinical condition is a fetal abnormality.

44 (withdrawn). The method of claim 43, wherein said fetal abnormality is selected from the group consisting of Trisomy 21, Trisomy 18, Trisomy 13, and Open Spina Bifida.

45 (withdrawn). The method according to claim 43, wherein said fetal abnormality is ectopic pregnancy, open spina bifida, neural tube defects, ventral wall defects, Edwards Syndrome, Patau's Syndrome, Turner Syndrome, Monosomy X or Klinefelter's Syndrome.

46 (withdrawn). The method of claim 43, wherein said clinical condition is an altered growth state selected from the group consisting of a growth promoting state and a growth inhibiting state.

47 (withdrawn). The method of claim 46, wherein said

clinical condition is selected from the group consisting of restenosis, atherosclerosis, wound healing, fibrosis, myocardial infarction, osteoporoses, rheumatoroid arthritis, multiple myeloma, or cancer.

48 (cancelled).

49 (withdrawn). A method for identifying an agent inhibiting the protease activity of pregnancy associated plasma protein A-2 (PAPP-A2), said method comprising the steps of

- i) incubating a) the polypeptide according to claim 12 and b) a predetermined substrate for said polypeptide, and c) a putative inhibitory agent, and
- ii) determining if proteolysis of said substrate is inhibited.

50 (withdrawn). The method of claim 49, wherein said substrate comprises a polypeptide.

51 (withdrawn). The method of claim 50, wherein said substrate comprises an internally quenched fluorescent peptide.

52 (withdrawn). The method of claim 50, wherein said substrate comprises IGFBP-5, or a fragment thereof.

53-54 (cancelled).

55 (withdrawn). A method for identifying an agent enhancing the protease activity of pregnancy associated plasma protein A-2 (PAPP-A2), said method comprising the steps of

- i) incubating a) the polypeptide according to claim 12 and b) a predetermined substrate for said polypeptide, and c) a putative enhancer agent, and
- ii) determining if proteolysis of said substrate is enhanced.

56 (withdrawn). The method of claim 55, wherein said substrate comprises a polypeptide.

57 (withdrawn). The method of claim 55, wherein said substrate comprises an internally quenched fluorescent peptide.

58 (withdrawn). The method of claim 55, wherein said

substrate comprises IGFBP-5, or a fragment thereof.

59-61 (cancelled).

62 (withdrawn). A method for purification of pregnancy associated plasma protein A-2 (PAPP-A2) or complexes of PAPP-A2 with other proteins, said method comprising the steps of

- i) providing a polyclonal or monoclonal antibody with specific binding affinity for a polypeptide according to claim 12,
- ii) purifying PAPP-A2 by means of affinity chromatography.

63-74 (cancelled).

75 (previously presented). The polypeptide of claim 12 wherein said polypeptide is the polypeptide according to (b).

76-82 (cancelled).

83 (previously presented). The polypeptide of claim 75 wherein said polypeptide comprises an amino acid sequence which differs from said sequence (a) solely by one or more conservative substitutions.

84-86 (cancelled).

87 (previously presented). The polypeptide of claim 12 wherein said polypeptide consists of amino acids 234 to 1791 of SEQ ID NO:2.

88-89 (cancelled).

90 (currently amended). An isolated polypeptide which is

- (1) a polypeptide consisting of an amino acid sequence which is (a) identical to residues 234-1791 of SEQ ID NO:2, or (b) a fragment, at least 5 amino acids in length, of mature PAPP-A2 (residues 234-1791 of SEQ ID NO:2),

where said fragment

- i) has a proteolytic activity against ~~specific at least for~~ Insulin Like Growth Factor Binding Protein 5 (IGFBP-5); and/or

ii) is recognized by an antibody, or a binding fragment thereof, which recognizes mature PAPP-A2; and/or

~~iii) competes with mature PAPP-A2 for binding to a cell surface receptor with an affinity for said mature PAPP-A2,~~

and where said fragment comprises

at least one of the following regions of SEQ ID NO:2:

Cys-403 to Cys-499

Cys-828 to Cys-881

Cys-1048 to Cys-1115

Cys-1390 to Cys-1396

Cys-1459 to Cys-1464

Cys-1521 to Cys-1525

Cys-1590 to Cys-1595

Cys-1646 to Cys-1653

Cys-1729 to Cys-1733

or

(2) a polypeptide which consists of a fusion of the polypeptide of (1) with an immunogenic carrier protein, or with a tag which may be used to facilitate the detection or purification of the fusion.

91 (previously presented). The polypeptide of claim 90 which is a fragment according to (1)(b).

92 (previously presented). The polypeptide of claim 91 which is a fragment, at least 17 amino acids in length, of mature PAPP-A2 (residues 234-1791 of SEQ ID NO:2).

93 (previously presented). The polypeptide of claim 91 which comprises at least 1169 consecutive amino acids of the polypeptide (mature PAPP-A2) consisting of residues 234-1791 of the polypeptide of SEQ ID NO:2.

94 (cancelled).

95 (previously presented). The polypeptide of claim 91 which comprises the elongated zinc binding consensus sequence (amino acids 733 to 743 of SEQ ID NO:2), LNR 1 (amino acids 586 to 612 of SEQ ID NO:2), LNR 2 (amino acids 619 to 644 of SEQ ID NO:2), LNR 3 (amino acids 1733 to 1758 of SEQ ID NO:2), SCR1 (amino acids 1396 to 1459 of SEQ ID NO:2), SCR2 (amino acids 1464 to 1521 of SEQ ID NO:2), SCR3 (amino acids 1525 to 1590 of SEQ ID NO:2), SCR4 (amino acids 1595 to 1646 of SEQ ID NO:2), SCR5 (amino acids 1653 to 1729 of SEQ ID NO:2), and all cysteine residues of mature PAPP-A2.

96 (previously presented). The polypeptide of claim 90 where the fragment is at least 50 amino acids in length.

97 (currently amended). An isolated polypeptide comprising

(I) amino acids 1-22 of SEQ ID NO:2, and

(II) a sequence selected from the group consisting of

(a) a sequence consisting of residues 234-1791 of SEQ ID NO:2, and

(b) a sequence which is at least 95% identical to (a) above,

where said polypeptide, or a cleavable fragment, of said polypeptide, which comprises ~~corresponding to~~ sequence (II) of said polypeptide,

i) has a proteolytic activity against Insulin Like Growth Factor Binding Protein 5 (IGFBP-5), ~~and/or~~

~~ii) is recognised by an antibody, or a binding fragment thereof, which recognizes a mature pregnancy associated plasma protein A-2 (mature PAPP-A2) polypeptide consisting of the amino acid sequence shown as amino acids 234-1791 of SEQ ID NO:2.~~

98 (currently amended). An isolated polypeptide comprising

- (I) amino acids 23-233 of SEQ ID NO:2, and
- (II) a sequence selected from the group consisting of
 - (a) a sequence consisting of residues 234-1791 of SEQ ID NO:2, and
 - (b) a sequence which is at least 95% identical to (a) above,

where said polypeptide, or a cleavable fragment, of said polypeptide, which comprises corresponding to sequence (II) of said polypeptide,

- i) has a proteolytic activity against Insulin Like Growth Factor Binding Protein 5 (IGFBP-5); ~~and/or~~
- ii) ~~is recognised by an antibody, or a binding fragment thereof, which recognizes a mature pregnancy associated plasma protein A-2 (mature PAPP-A2) polypeptide consisting of the amino acid sequence shown as amino acids 234-1791 of SEQ ID NO:2.~~

99 (currently amended). An isolated polypeptide comprising

- (I) amino acids 1-233 of SEQ ID NO:2 and
- (II) a sequence selected from the group consisting of
 - (a) a sequence consisting of residues 234-1791 of SEQ ID NO:2, and
 - (b) a sequence which is at least 95% identical to (a) above

where said polypeptide, or a cleavable fragment, of said polypeptide, which comprises corresponding to sequence (II) of said polypeptide,

- i) has a proteolytic activity against Insulin Like Growth Factor Binding Protein 5 (IGFBP-5); ~~and/or~~
- ii) ~~is recognised by an antibody, or a binding fragment thereof, which recognizes a mature pregnancy~~

~~associated plasma protein A-2 (mature PAPP-A2)
polypeptide consisting of the amino acid sequence
shown as amino acids 234-1791 of SEQ ID NO:2.~~

100 (previously presented). The polypeptide of claim 91 which is a fragment of mature PAPP-A2 which results from intracellular proteolysis.

101 (previously presented). The polypeptide of claim 99 which consists of the amino acid sequence of SEQ ID NO:2.

102-104 (cancelled).

105 (previously presented). The polypeptide of claim 12 where said insertions or deletions, if any, are of 1 to 5 amino acid residues.

106-107 (cancelled).

108 (previously presented). The polypeptide of claim 12 which is a fragment of mature PAPP-A2 (234-1791 of SEQ ID NO:2).

109 (cancelled).

110 (new). An isolated polypeptide which

(a) consists of residues 234-1791 of SEQ ID NO:2; or

(b) differs by not more than 16 insertions and/or deletions and/or substitutions from the polypeptide of (a), where said polypeptide has a proteolytic activity against Insulin Like Growth Factor Binding Protein 5 (IGFBP-5).

111 (new). An isolated polypeptide which

(a) consists of residues 234-1791 of SEQ ID NO:2; or

(b) is at least 99% identical to the polypeptide of (a), and which consists of 1548-1568 amino acids.